Workshop on Counter-Terrorism Products Regulated by CBER: Efffective Strategies to Assist in Product Development

– OBRR Perspective on Clinical Development Phase

L. Ross Pierce, M.D.
Clinical Review Branch, Div. Of Hematology, Office of Blood Research & Review, CBER, FDA

The Problem

- Provide substantial evidence of safety and efficacy when subjects infected/intoxicated with the target agent are not available.

The Solution

- Provide evidence of efficacy in *appropriate* animal models (e.g., “Animal Rule”).
- Provide data to support the choice of animal models and to help bridge animal data to the human situation, including:
  - Comparative pathophysiology and natural history of target disease in the respective species
  - Comparative PK of drug in blood; tissue levels
  - Compare concentrations of pathogen/toxin across species.
- Provide human safety and PK data in healthy volunteers.

Overall strategies for development of CBT Biologics

- Decide which indication(s) will be sought and in what order.

  Example: Anthrax Ig + antibiotic

  - Pre-exposure prophylaxis
  - Post-exposure prophylaxis

- Therapy at early-, middle-, or late-stage disease
- Monotherapy or combination therapy?

Focus Development Plan

- **Early crafting of a draft INDICATIONS AND USAGE section of the eventual package insert can help focus clinical development**

The urgency of the perceived threat may drive the timeline of product development

- **–Fast Track if providing unmet medical need to treat serious and/or life-threatening aspect of disease.**
- **–Sequential vs. Parallel Pre-Clinical and Clinical Testing depending on circumstances (e.g., Anthrax Immune Globulin) . *Agency flexibility will be determined case-by-case*.**

Timeline of product development

- **“Contingency protocol” Treatment IND once human safety, PK, and basis for concluding substantial evidence of efficacy are available may be appropriate.**
- **Phase 4 Confirmation of Efficacy and Appropriateness of Dosing Regimen *in the event of* bioterrorism event involving the agent being targeted.**

Anthrax Immune Globulin as an Example of a CT Clinical Product Development Plan

- **Plan developed during 2001 U.S. Anthrax Episode (*Assumed Ongoing New Cases* of Inhalational Anthrax)**
- Need: Inhalational anthrax carried historical ~90% mortality rate with antibiotic therapy (5/11 in 1991).
- Rationale for adjunctive use of Ig product to inactivate pre-formed and well-characterized anthrax toxins based on other disease models (tetanus, etc.)
- Anecdotal historical use of crude AIG/AIP products in inhalational anthrax of little value.
- Considered both human and animal Ig products.

Anthrax Immune Globulin as an Example of a CT Clinical Product Development Plan

1. **Prepare product using well-accepted methodologies.**
2. **Conduct proof-of-concept/activity study in animals.**
3. **If #2 successful, consider conducting preclinical efficacy, preclinical PK, clinical safety, and clinical PK simultaneously rather than sequentially (case-by-case basis).**

Clinical Phase *of Anthrax Immune Globulin Clinical Product Development Plan*

- **1. Single-dose dose-ranging safety/tolerability and PK study in normal volunteers (or in patients with confirmed cutaneous anthrax).**
- **2. Single-dose dose-ranging safety/efficacy phase II multicenter "field" treatment IND study in patients with strongly suspected or confirmed inhalational anthrax.**

Clinical Phase *of Anthrax Immune Globulin Clinical Product Development Plan*

- **3. Repeat dose dose-ranging safety/efficacy phase II treatment IND multicenter "field" study in patients with strongly suspected or confirmed inhalational anthrax.**
- **4. Phase III safety/efficacy treatment IND study. This might be a continuation phase of #1 or #2 or #3 above.**

Anthrax Immune Globulin – Pharmacokinetic (PK) Considerations

- Single dose tolerability/PK study of an IV product in normals should evaluate the $AUC_{(t}$), $AUC_{(infinity}$), C_{max}, Clearance, Vol of Distribution, and half-life. PK model should be pre-specified.
- Single dose tolerability/PK study of an IM or SC product should also evaluate T_{max}.
- Optional PK data in patients with inhalation anthrax in subset of phase II study subjects.

Anthrax Immune Globulin as an Example of a CT Clinical Product Development Plan

- **Number of doses studied product-specific.**
- **Depending on perceived urgency, in the phase I single-dose tolerability and PK study the 2 lowest unstudied dosage groups might be studied in parallel (e.g., 1 cohort dosed at x mg/kg while another cohort receives 3x mg/kg). When safety data deemed satisfactory for those cohorts, the next 2 dosage levels could be studied either sequentially or in parallel.**

Anthrax Immune Globulin as an Example of a CT Clinical Product Development Plan

- **Stratify Subjects by Stage of Inhalation Anthrax.**
- **• Early (flu-like syndrome with known inhalation exposure)**
- **• Middle (dyspnea or chest pain without alternative explanation in conjunction with stated typical symptoms and strongly suspected exposure)**
- **• Late (hypoxemia, respiratory failure, hypotension, meningitis, widened mediastinum and/or pleural effusion on CXR). Patients with meningitis should also be analyzed as a subgroup.**
- **Product might prove most effective in early disease where burden of anthrax toxin least.**

Anthrax Immune Globulin as an Example of a CT Clinical Product Development Plan

- **For subjects with very early suspected but unconfirmed disease and only flu-like syndrome including fever, it can be argued that a placebo-control + antibiotic is ethical and appropriate (low risk, add-on tx)**
- **For subjects with Middle or Late-stage disease, a randomized dose-ranging design may be most appropriate.**
- **Dose ranging especially important with large population exposure requiring large quantities of product. Knowledge of the minimum effective dose would be key.**

Anthrax Immune Globulin as an Example of a CT Clinical Product Development Plan

- **If active-only dose-ranging design employed, the highest and lowest doses should differ substantially (e.g., 10-50 fold) and should include a probably less-than-fully therapeutic dose in combination with antibiotic.**

Anthrax Immune Globulin – Efficacy Analyses

- The primary efficacy variable: survival/total mortality either as a proportion or as time to death.
- Secondary efficacy variables include:
  - days in ICU
  - hospitalization duration
  - respiratory failure (requirement for mechanical ventilation)
  - need for vasopressors.
- Additional clinical variables would include time between exposure, onset of illness, initiation of antibiotic therapy, and initiation of Anthrax Ig.

What to include in original IND submission

- - Overall clinical development plan, including
  - Specific Indication(s) to be sought
  - Plans for phase I, II, III, and IV studies, if applicable, including finished (not draft) protocol for initial human trial.

What to include in original IND submission

- -Justification for the starting and maximum doses for the initial human tolerability studies.
- -Discuss relevance of chosen animal species for any animal efficacy/proof of concept studies.
- May include comparative animal and anticipated human pharmacokinetic data.
- Complete data including line listings of any prior human use.

Considerations for design of phase 2/3 safety and PK clinical studies

- o The design and analyses of the study should be prospectively defined in the protocol.
  - o The dose and dosing schedule for the proposed studies should be justified.
- o The data analyses presented in the BLA should be consistent with the analytical plan submitted to the IND.
- o Obtain and analyze appropriate secondary endpoints including candidate surrogate efficacy outcome variables.

Considerations for design of phase 3 safety and PK clinical studies

- o Secondary endpoints and their corresponding statistical analyses should be prospectively defined in the study protocol.
- o For studies employing randomization (such as different doses of study drug), the study's power to detect differences in the overall incidence of adverse events (AEs) between study arms should be stated in the protocol.

Considerations for design of phase 3 safety and PK clinical studies

- The protocol should state the minimum true incidence of an adverse effect that the study has 95% power to detect.
- o The size of the PK study should be justified (generally ~ 20 subjects).
- - When fewer subjects needed to characterize PK than are needed to characterize product safety, consider separate or nested PK study design.

Safety analyses

- • number of test product administrations by subject
- • number of adverse experiences (AEs) reported at any time during the study irrespective of opinions concerning relatedness to administration of the investigational agent
- • number of adverse experiences temporally associated with infusions

Safety Analyses (cont.)

- - number of infusions temporally associated with one or more adverse experiences.
- - the proportion of infusions for the trial population for which “infusional” AEs have been reported and
- - the proportion of subjects who experience one or more AEs at any time during the course of the trial.

Adverse Events and Product Infusion Rate

- Begin with a slow infusion rate and titrate upward according to a pre-specified *forced titration* scheme as tolerated.
- Analyze AEs as a function of both dose and infusion rate (for IV products).
- The CRF must provide a space for recording the infusion rate at the time AEs are first noted to permit AE analysis by infusion rate.

Safety Endpoints for Trials of Ig Products

- Serious hypersensitivity reactions
- Renal insufficiency
- Aseptic meningitis
- Thrombosis and other SAEs
- Severe AEs
- All other AEs
- Vital signs, physical exams (repeated) routine chemistry, hematology, UA.
- Monitor for seroconversions and NAT for HIV 1&2, HBV, HCV, Parvovirus B19 in normals.

Considerations for design of phase 3 safety and PK clinical studies

- Use subject diaries kept current in “real time” as essential source documents for the complete collection of AE data.

- Data in subject diaries should support corresponding case report forms (CRF) entries and study database.

CT Clinical Product Development Plan Summary

- Develop both focused initial and long-term clinical development plans
- Be flexible in tailoring your development plan to the specific disease/drug and/or biologic combination, good science, and what is feasible.
- Consult periodically with FDA to keep abreast of CBER Current Thinking regarding evolving data and how they may affect your development plans.
- Have a detailed statistical analysis plan and stick to it.
- Insure adequate study monitoring to help avoid GCP-related product approval delays.

CT Clinical Product Development Plan Summary (cont.)

- Develop Phase III/IV contingency protocols to
  - Provide expanded use
  - Validate efficacy in target disease/population
  - Validate adequacy of dosing regimen
  - Validate safety in patients with target disease.